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Outcomes in liver transplantation: Does sex matter?

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Summary

A growing literature has highlighted important differences in transplant-related outcomes between men and women. In the United States there are fewer women than men on the liver transplant waitlist and women are two times less likely to receive a deceased or living-related liver transplant. Sex-based differences exist not only in waitlist but also in post-transplant outcomes, particularly in some specific liver diseases, such as hepatitis C. In the era of individualized medicine, recognition of these differences in the approach to pre and post-liver transplant care may impact short and long-term outcomes.

Keywords

Liver transplantation; Sex; Women's health; Hepatitis C virus; Waitlist outcome; Quality of life; Liver allocation; MELD score

Introduction

A growing literature has highlighted important differences in transplant-related outcomes between men and women. In the United States, there are fewer women than men on the liver transplant (LT) waitlist (38% *vs.* 62%) [1], and women are two times less likely to receive a deceased or living-related LT [2–4] (Fig. 1). While the MELD-based allocation system has decreased waitlist mortality by prioritizing the sickest patients awaiting LT [5], sex-based disparities in waitlist outcomes (Fig. 2) have not been overcome. Indications for transplant

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Conflict of interest

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Author contribution

All authors contributed to the literature review, analysis and interpretation of the data. Monika Sakar compiled the first draft of the manuscript which was then critically reviewed by the remaining authors.

(Figs. 3 and 4) and their respective disease course post-LT also vary by sex. This review focuses on the current knowledge of transplant-related outcomes in women with the goal of facilitating a more gender-specific management of transplant patients.

Age at transplant

Both men and women are most commonly transplanted between 50 and 64 years of age, though a somewhat higher percentage of women are transplanted in the older and younger age ranges. Among U.S. LT recipients in 2012, approximately 15% of women were transplanted at >65 years of age compared to 13% of men, and approximately 7% of women compared to 4% of men were transplanted between ages 18 and 34 years [1].

Transplant rates and waitlist mortality

Women remain disadvantaged in the post-MELD era with worse waitlist outcomes (Table 1) [6–9], with women 30% less likely than men to receive a transplant within 3 years of listing (OR 0.7; 95% CI 0.6–0.8; p <0.001) [9]. A recent US investigation of trends in LT rates found that in the pre-MELD era, women had a 9% lower adjusted transplant rate compared to men, which increased to a 14% difference (p <0.004) after implementation of MELD. The lower transplant rates among women compared to men appeared to predominate at higher MELD scores with 20% lower rates at MELD scores 20–29 and a 12% lower rate at MELD scores of 30–40 (p values <0.05). However, similar transplant rates were noted at MELD scores <15 [9]. Disparities in transplantation rates may translate into higher healthcare expenditures for waitlisted women, given the longer wait times and lower risk of non-liver-related removal from the waitlist [9,10].

Recent data investigating the rate of waitlisting relative to those potentially eligible for transplant, have found that women may have greater access to the transplant waitlist, despite lower rates of transplantation than men [9,11]. These data also highlight an ongoing racial/ethnic disparity for Hispanics, who have lower transplant rates compared to other racial/ethnic groups in the post-MELD era, although sex-based disparities in transplant rates by race/ethnicity have not specifically been identified [11].

Women have also been shown to be at higher risk of death or becoming too sick for LT (OR 1.3; 95% CI 1.1–1.5; p = 0.003) [7] (Fig. 2). This higher risk of waitlist mortality in women has been observed in most [12,13], but not all studies [9]. There are several hypotheses to explain sex differences in waitlist outcomes. A major focus has been on renal function measures. It has been proposed that less muscle mass in women results in lower creatinine levels for similar degrees of renal impairment than men, resulting in overall lower MELD scores [14,15]. Though creatinine levels do contribute to sex differences in waitlist outcomes, studies adjusting for estimated glomerular filtration rate (eGFR), and thereby accounting for gender differences in renal function, reveal persistent disparities in liver allocation and waitlist mortality [8,12,14]. In a study using iothalamate as a direct measure of GFR in wait-listed patients, women were more likely than men to have a pre-transplant GFR <60 ml/min (29% *vs.* 21%) and <30 ml/min (10% *vs.* 6%, respectively) [16]. A U.S.-based study in the post-MELD era (n = 42,322) noted similar overall waitlist mortality, but

among patients with non-dialysis dependent End Stage Renal Disease (ESRD), women were more likely to die on the waitlist than men (26% *vs.* 20%; $p = 0.001$) [17]. Moreover, despite lower GFR levels, women were less likely to receive dialysis [18], and lower rates of dual liver-kidney transplant were reported in women compared to men with non-dialysis dependent ESRD (OR 0.5; $p < 0.001$) [19].

Another potential reason for the higher waitlist mortality among women relates to physical stature. Deceased donors are more often male, thus with size matching, more likely to be allocated to men. In addition, preferential allocation of small or split livers to children may also limit the pool of available organs for women, contributing to longer waitlist times and higher risk waitlist dropout [6]. A UNOS-based study found that women had a 20% higher risk of death than men, after adjusting for age, region, blood type, disease etiology, race, and MELD but this difference largely disappeared with the addition of height to the model (HR 1.04; 95% CI 0.98–1.1; $p = 0.2$) [13]. Another UNOS-based study found that although women were 25% less likely to undergo LT in a given month compared to men, this decreased to 17% with adjustment for renal function, and to 13% with further adjustment for liver volume [6]. These data suggest that like renal function, physical stature contributes to, but does not fully explain sex differences in waitlist outcomes.

Interestingly, while 35% of deceased-donor LT recipients are women, 44% of live donor transplants are in female recipients. The higher percentage of women receiving a live as compared to deceased donor transplant may be reflective of their smaller stature, and therefore better suitability for smaller, live donor grafts [1].

The implications of these findings are several-fold. First, continued efforts to find markers of renal function that are gender independent are essential. Second, nephrologists need to consider gender differences in their recommendations for renal replacement therapy and kidney transplant. Third, women should be encouraged to pursue living donation, and programs may need to consider splitting more organs to offset the longer wait times for women. Finally, continued evaluation of gender disparities as the MELD system evolves is critical for affecting outcomes in waitlisted women and informing future allocation policy.

Post-transplant outcomes

Patient and graft survival

Whether there are sex differences in post-transplant survival, remains controversial. A recent study from Germany (n = 266) found that female sex in the post-MELD era was a strong and independent risk factor for 90-day post LT mortality (OR 3.2; 95% CI 1.3–7.6; $p = 0.009$). Women had higher MELD scores at transplant than men in this study, and higher post LT mortality was only identified among individuals with pre-transplant MELD scores >20 (33% *vs.* 14%; $p < 0.05$), and not among those with MELD scores <20 (10 *vs.* 4%; $p > 0.05$) [20]. Recent data from the U.S. Scientific Registry of Transplant Recipients (SRTR) (n = 19,249) found higher donor risk indices in women than men (1.46 *vs.* 1.4; $p < 0.001$), with a 24% higher odds among women receiving a low quality graft (OR 1.24; $p < 0.001$). This is possibly driven by use of smaller grafts allocated to women, but with no difference in graft survival between women and men after adjustment for differences in graft quality [21].

Donor gender has also been investigated as a factor influencing graft survival. Older studies report worse post-LT survival in gender mismatched transplants, with particularly high risk of graft loss noted in male recipients of female donors [22,23]. Recent data from Germany noting higher post-transplant mortality in women did not identify donor gender mismatch as a contributing factor [20]. Other studies indicate that donor quality, rather than donor gender or sex mismatch are more important in predicting graft survival. In composite, it remains unclear to what extent sex mismatch or receipt of a female donor, contribute to potential differential post-transplant outcomes.

Rejection

The immune profile of men and women are distinct, with women having been described as more “immunogenic” than men, with greater antibody production and higher rates of autoimmune conditions [24]. Sex differences in immune activity may also translate into different post-transplant immunosuppression needs. A recent multicenter trial investigating immunosuppression withdrawal after LT identified male sex as an independent predictor of successful weaning and subsequent development of immune tolerance (OR 4.7; $p = 0.016$) [25]. Interestingly, the opposite may hold true in the pediatric population, and maternal grafts in female recipients may also protect against rejection in children with biliary atresia [26,27]. In the hepatitis C population, female gender has been shown to predict early acute rejection (HR 1.8; 95% CI 1.2–2.7; $p = 0.004$) [28]. Although older studies suggest that female recipients of male livers may be predisposed to chronic rejection, in studies that include all liver conditions no definitive sex differences in risk of acute or chronic rejection have been demonstrated [29–31].

Renal dysfunction

Female sex has been shown to be an independent risk factor for post-transplant renal impairment [32–34] for similar reasons as described above. While earlier studies have been limited by use of indirect measures of renal function, a recent study using iothalamate as a direct measure of GFR also identified female sex as an independent predictor of Pstage 3 CKD at 1 (OR 3.0; 95% CI 1.7–5.1; $p < 0.001$) and 5 years post-transplant (OR 2.5; 95% CI 1.3–4.7; $p = 0.004$). This finding appeared to be related to worse renal function in women compared to men in the pre-transplant setting [16].

Sarcopenia or physical condition

Recent data indicate that sarcopenia, or severe muscle depletion, is strongly associated with waitlist mortality, but with men at greater risk than women (OR 5.9; 2.4–14.6; $p < 0.001$) [35]. Pre-transplant muscle mass is also emerging as an important predictor of post-transplant outcomes. A study of 338 transplant candidates (223 men, 115 women) found that low muscle mass as determined by CT scan was strongly associated with post-transplant length of ICU stay, total length of hospital stay, and number of days requiring intubation, although this effect was modest in women and quite strong in men. In men, but not women, low muscle mass was also associated with worse post LT survival and hospital disposition [36,37]. The differential effect may be related to greater baseline muscle mass in men for whom a greater degree of cachexia and catabolism is reflected in the presence of sarcopenia, though further investigation is required.

Quality of life

Data on sex differences in overall quality of life (QOL) after LT have been conflicting [38]. Older studies found no differences [39,40] whereas more recent data report lower QOL scores at 1 and 2 years in women compared to men [41], as well as worse psychosocial adjustment in women [42]. In contrast, a small study (n = 52) of patients transplanted for hepatitis C virus (HCV) found that women had significantly better mental health, emotional role functioning, as well as lower pain scores than men, whereas men felt they had better physical functionality after LT [43]. A larger post LT cohort (n = 386) including all liver diseases noted worse measures of physical distress and personal function in women, without apparent sex differences in psychological distress or general health perception [44]. Despite different methodologies for measuring specific QOL indictors, the overall findings indicate that sex differences in post LT QOL are apparent.

Cirrhosis is known to impair sexual function, an important QOL measure. Most men and women experience improved sexual function after LT [45], though one large study of 233 transplanted women found no improvement in multiple measures of sexual satisfaction following transplant [46]. *De novo* sexual dysfunction following LT has been identified in 33% of men and 26% of women (p value not reported) [47]. Persistent sexual dysfunction following transplant may relate to depression, and psychosocial interventions in the post LT setting may be underutilized [48]. Interestingly, a recent study found that marital happiness was not affected by LT in men, while women in the post LT setting experienced marked improvement in conjugal satisfaction, which correlated with sexual function in women ($r = 0.4$; $p = 0.02$), but not in men ($r = 0.1$; $p = 0.3$) [45]. Chronic anovulation and symptoms of premature menopause are common problems in women with end-stage liver disease and most pre-menopausal women do have restoration of ovarian function and fertility after transplant [49]. Pregnancy outcomes in the post-LT setting have been well studied, though beyond the scope of the current review [50–53].

Non-hepatic complications following liver transplantation

With increased life expectancy, *de novo* tumors and cardiovascular disease are now leading causes of non-graft related death in long-term liver transplant survivors [54–56]. This high incidence of non-hepatic events is theoretically explained by the presence of pre-existing risk factors, as well as the introduction of additional risk factors associated with the organ transplant process, such as chronic exposure to immunosuppressive agents, life-style habits (weight gain, tobacco use), and/or the development of *de novo* metabolic disorders including post-transplant arterial hypertension, diabetes and/or dyslipidemia. With respect to cardiovascular risk factors and disease, no gender association has been found in most studies to date [54,57]. Interestingly, the fact that male gender is a known risk factor for malignancy in the general population but not in post-transplant studies suggests that women have closed the gap, and hence are at higher risk than women in the general population.

Overall, the risk of malignancy is 2 to 4 times higher in transplant recipients than in an age- and sex-matched population [58–62]. With the exception of a few studies where men appear to be more affected than women [62–65], there does not appear to be a clear gender-based difference in the incidence of *de novo* malignancy. Importantly, since the incidence rates of

breast cancer is not increased in organ transplant recipients, there is no evidence to suggest the need for breast cancer screening that would differ from the general population [54].

Post-transplant outcomes in specific liver diseases (Table 2)

Chronic hepatitis C

Chronic hepatitis C is an important cause of cirrhosis and hepatocellular carcinoma (HCC) globally. In the United States, Europe and Japan, HCV is the most common indication for LT. In recent years, the proportion of patients with HCC as the primary indication for LT has increased, likely reflecting prioritization of small HCC for LT as well as the increased prevalence of cirrhosis among HCV-infected persons [66,67]. Cirrhosis and its complications are less frequent in women than men [67] and this difference is likely due to the higher rates of spontaneous clearance among women [68], the protective effects of estrogens on fibrosis in premenopausal women [69], as well as lower frequency of cofactors associated with fibrosis in women, such as heavy alcohol use.

Recurrent disease is essentially universal among viremic patients after LT and the estimated median time to recurrent cirrhosis is 8–10 years [70] with rapid progressors advancing to cirrhosis within 3–5 years [71]. Approximately 10% develop severe early recurrence with cholestatic features within the first year post LT, which can rapidly progress to graft loss in the absence of antiviral therapy. Higher rates of severe HCV disease and reduced graft survival are associated with several recipient and donor factors, including African-American race, HIV co-infection, older donor age and IL28B polymorphisms. Women have more severe recurrent disease [72–74] with a 23% higher risk of advanced fibrosis than men after a median of 3 years after liver transplant [72]. Viral eradication prior to or after LT can prevent complications of HCV recurrence. Few studies have focused on sex differences in response to therapy, but the lower response rates to interferon-based therapy in women [75] are likely due to lower adherence to therapy and a higher rate of therapy discontinuation related to ribavirin-induced anemia. Sex differences in treatment response with direct acting antiviral therapies have not been studied, but the greater risk of ribavirin-associated toxicity may continue to limit therapy tolerability and efficacy in women (Table 3).

Non alcoholic fatty liver disease (NAFLD)

Non-alcoholic steatohepatitis (NASH) is the third most common indication for LT in the United States and is predicted to surpass HCV as the most common indication for LT in 10 years' time [76]. Most population-based studies note a higher prevalence of NAFLD in men, though clinically diagnosed and biopsy proven NASH appears to be higher in women [77–79]. Hormonal factors may contribute to this difference, as a recent cross sectional study noted increased liver fibrosis in men with NASH compared to pre-menopausal women, but similar fibrosis scores as postmenopausal women [80]. Sex differences in NAFLD prevalence may also equalize after women reach menopause [81,82]. Patients receiving LT for NASH are equally distributed by sex [78], with no apparent sex differences in post LT patient or graft survival [83,84], or risk of recurrent NASH [85,86].

Alcoholic liver disease (ALD)

There are clear sex differences in the hepatotoxic effects of alcohol, with higher risk of hepatic damage at lower doses of alcohol exposure in women (>10 g daily) compared to men (>20 g daily) [87]. This is in part related to lower levels of gastric alcohol dehydrogenase in women, which is involved in first pass alcohol metabolism [88]. Once diagnosed with ALD, women have more rapid acceleration of liver fibrosis than men, which may persist even after alcohol cessation [89]. Consistent with this finding, men on the waiting list for ALD tend to have longer median durations of alcohol abuse than women [90,91]. However, the overall prevalence of ALD remains higher in men, and a greater proportion of men undergo LT for ALD [90,92,93]. UNOS-based data from 2002 to 2012 indicate that men account for 75% of patients transplanted for a primary diagnosis of ALD [78].

Most studies have not identified sex differences in post LT graft or patient survival for ALD [91,93], though one older study noted a higher percentage of women than men surviving at 5 years (78% *vs.* 58%, respectively, no *p*-value provided) [94]. A French study identified *de novo* malignancies as an independent risk factor for lower post LT survival in ALD and though sex was not predictive on multivariate analysis, male sex was strongly associated with the risk of *de novo* malignancy [93].

Data on sex differences in recidivism rates are conflicting. A Scandinavian study (n = 103) found no association between sex and recidivism [95], while a Canadian study (n = 80) noted higher recidivism in women, accounting for 5/8 patients that resumed problem drinking. Interestingly, 4/5 of these women had a pre-transplant diagnosis of depression, which may contribute to the higher observed recidivism in women [96]. A U.S.-based study has since reported depression to be a strong predictor of post LT recidivism, though sex was not specifically investigated in this model [90].

Autoimmune hepatitis (AIH)

Like most autoimmune conditions, AIH is more prevalent in women than men, with a sex ratio of 3.6:1 [97]. Women comprise the majority of patients that receive LT for AIH, though a recent study (n = 1318) identified male sex as an independent predictor of mortality or need for LT (HR 1.5 compared to women, 95% CI 1.2–2.2; no *p*-value reported). In this study, cirrhotic women with AIH also had a lower HCC incidence rate per 1000 person-years compared to men (0.6 *vs.* 5.5) [98]. A smaller study (n = 138) noted a higher unadjusted risk of cirrhosis at the time of AIH diagnosis in men than women (OR 2.8; 95% CI 1.2–6.2; $p = 0.01$) though risk of mortality or need for LT was not different [99]. Interestingly, there are no apparent recipient sex differences in risk of *de novo* autoimmune hepatitis (HR 0.8; 95% CI 0.3–2.3; $p = 0.7$), although the risk of *de novo* AIH appears to be higher in recipients of female donors regardless of recipient sex (HR 3.0; 95% CI 1.1–8.3; $p = 0.03$) [100]. To date, sex differences in risk of post LT survival, recurrent AIH, or risk of rejection have not been identified [101–103].

Primary biliary cirrhosis (PBC)

Like AIH, PBC is more common in women accounting for ~90% of PBC cases [104]. Women with PBC tend to be younger at the time of diagnosis, with worse fatigue and pruritus than men, and higher risk for concomitant autoimmune conditions. Interestingly, recent data note similar fatigue and cognitive symptoms in women after LT compared to sex matched non-transplant controls (p values >0.05), whereas transplanted men compared to non-transplant controls had worse fatigue (p <0.05) and cognitive symptoms (p <0.005) [105]. Pre-LT serologic profiles are similar in men and women, though men have more progressive disease and overall worse outcomes [101,106,107]. A recent large study (n = 2,353) found that men were less responsive to ursodeoxycholic acid, based on ALT, total bilirubin and alkaline phosphatase levels (OR 0.9; 95% CI 0.83–0.97; p = 0.007) [108]. Similar to most chronic liver diseases, the incidence of HCC in PBC patients with cirrhosis is lower in women than men, with a recent study noting a 10-year HCC incidence of 2.0% in women *vs.* 6.5% in men (p <0.001) [109–112]. Though HCC in women is predominantly seen in cirrhosis, men with PBC have been diagnosed with HCC at all stages of fibrosis [112]. Data are limited on post LT sex differences in patient or graft survival, though recurrent PBC or risk of rejection appears to be similar between sexes [101,113].

Primary sclerosing cholangitis (PSC)

Unlike PBC and AIH, PSC is less common in women, with more than 60% of cases diagnosed in men, and no major differences in clinical presentation [114]. While most studies have not identified a difference in overall survival [115,116] a regional study from Sweden (142 men and 57 women) identified female sex as a strong and independent risk factor for death or need for LT (RR 2.0; 95% CI 1.1–3.7; p = 0.02) [117]. The reasons for the discrepancy in survival outcomes between this and other studies are not clear, but may be related to delayed diagnosis in women as this condition is more typically associated with men. Sex differences in genetic factors contributing to PSC-related outcomes have been identified. The rs738409 variant (I148M) of the *PNPLA3* gene was recently shown to predict survival in patients with PSC with concurrent dominant strictures, although this effect was restricted to men (mean survival 11.9 years in I148M carriers *vs.* 18.8 years in wildtype; p <0.001), and did not predict survival in women (p = 0.65) [118].

Data reporting sex differences in post LT outcomes in PSC are limited. A single center study (n = 83) noted a smaller proportion of women than men with post LT biliary complications, revisions of the transplanted liver, and/or death (32% *vs.* 65%, p = 0.02) [119]. To date, no studies have demonstrated differences in risk for recurrent PSC on adjusted analyses [120–122] or differences in risk of rejection [101]. A study of 61 women and 119 men following LT for PSC identified a higher incidence of *de novo* colorectal cancer in women (SIR 17.6; 95% CI 3.6–51.4) [123], though other studies have not identified sex differences in risk of post LT malignancy for patients with PSC [124,125].

Hepatocellular carcinoma

The risk ratio of HCC in cirrhotic women *vs.* men ranges from 1:2 to 1:4 [126]. Sex differences in HCC risk also extend to chronic non-cirrhotic HBV infection for which the AASLD recommends initiation of HCC screening in non-cirrhotic Asian women at age 50

years compared to 40 years in Asian men [127]. A large Italian study (482 women and 1352 men) investigating all etiologies of liver disease found that women were older at HCC diagnosis, had higher alpha-fetoprotein levels, and were more likely to have smaller, unifocal and well-differentiated HCCs, with lower likelihood of presenting with metastases. Though overall survival was better in women than men, there were no differences in likelihood of undergoing curative treatment such as transplant or resection. In this study survival differences disappeared when subgroup analyses were performed among individuals diagnosed with HCC by surveillance imaging opposed to symptomatic presentation, suggesting that sex differences in presentation and outcomes may have been related to differential receipt of HCC surveillance, rather than sex differences in tumor biology [128]. In a recent study from the U.S. Surveillance, Epidemiology, and End Results database, women with HCC were found to have a significantly greater median overall survival compared with men, independent of age, race, disease stage, or treatment (11 *vs.* 10 months; HR 0.93; 95% CI, 0.91–0.96, $p < 0.001$). Interestingly, greater survival in women was noted among those who received surgical resection (HR 0.87; 95% CI 0.78–0.96; $p = 0.01$) but not among those receiving liver-directed therapy or LT [129]. In another U.S.-based study women were more likely to receive curative resection than men. Though adjusted analyses revealed lower risk of decompensation in women than men (OR 0.79; $p < 0.001$), these authors found that among those with compensated cirrhosis and HCC, women were still more likely to be offered curative therapy. No differences in rates of LT were noted for patients with HCC, similar to previously reported UNOS data [7,130]. In the latter study, tumor characteristics were not available, therefore higher rates of resection in women may be related to lower tumor burden, as demonstrated in the Italian study [128]. Recipient sex does not appear to predict risk of recurrent HCC post LT [131–133].

Acute liver failure

A high female predominance is observed in acute liver failure of most etiologies, not only those associated with autoimmunity, though the reason for this association is not clear. In particular, acute liver failure due to Wilson disease occurs predominantly in young females with a female to male ratio of 4:1. Furthermore, approximately 10% of patients with hepatotoxicity due to medical/recreational drugs or herbal products may progress to fulminant hepatic failure, potentially requiring LT. While sex does not seem to increase the overall risk of drug-induced liver injury, the severity may differ by sex, with a predominance of severe cases observed in women [134–136].

Conclusions

LT remains the optimal treatment for patients with end-stage liver disease, though sex differences in access to transplant persist. In this review, we highlight sex-based disparities in transplant outcomes, as well as sex differences in transplant indications, some of which are quite marked and others more subtle. Despite clear differences in waitlist outcomes, the reasons for this particular disparity remain only partially understood. Further data are clearly needed to narrow the gender gap in transplant-related events, and to facilitate interventions that may optimize the management of women in both the pre- and post-transplant period.

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Abbreviations

MELD	model for end-stage liver disease
QOL	quality of life
LT	liver transplantation
IFN	interferon
RBV	ribavirin
HCC	hepatocellular carcinoma
eGFR	estimated glomerular filtration rate
SRTR	Scientific Registry of Transplant Recipients
HCV	Hepatitis C virus
NAFLD	non-alcoholic Fatty Liver Disease
NASH	non-alcoholic steatohepatitis
ALD	alcoholic liver disease
AIH	autoimmune hepatitis
PBC	primary biliary cirrhosis
PSC	primary sclerosing cholangitis

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Key Points

- Transplant indications, waitlist outcomes, and post-transplant course vary by sex
- Waitlist outcomes (liver allocation and waitlist mortality) remain worse in women in the post model for end-stage liver disease (MELD) era, particularly at high MELD scores. Inadequate renal function measures that underestimate renal impairment in women, as well as differences in physical stature contribute to, but do not fully explain sex differences in waitlist outcomes
- Despite different methodologies for measuring specific quality of life (QOL) indicators, the overall findings indicate that women have lower QOL scores post-liver transplantation (LT) compared to men
- While overall post-transplant graft and patient survival do not seem to differ by sex, in some specific liver diseases, particularly in hepatitis C, sex differences are evident (more severe recurrent disease and lower response rates to interferon-ribavirin based therapies in women)
- Data on sex differences in alcohol recidivism rates are conflicting
- Recipient sex does not appear to predict risk of recurrent hepatocellular carcinoma (HCC) post-LT

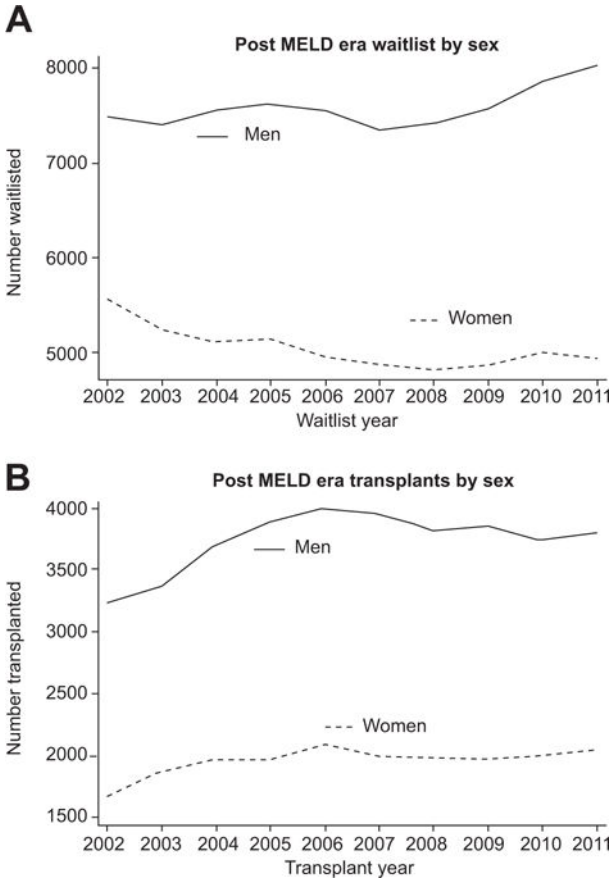


Fig. 1. Post-MELD era waitlist and transplant numbers by sex

(A) Post-MELD era waitlist by sex. Number of women and men in the U.S. listed for liver transplant based on data from the Scientific Registry of Transplant Recipients (SRTR) in the post-MELD era. (B) Post-MELD era transplant numbers by sex. Number of women and men receiving live and deceased donor liver transplants in the U.S. based on SRTR data in the post-MELD era.

Fig. 2. Post-MELD era waitlist mortality by sex

Number of deaths among women and men in the U.S. based on SRTR data in the post-MELD era. Those delisted as too sick for transplant are not included.

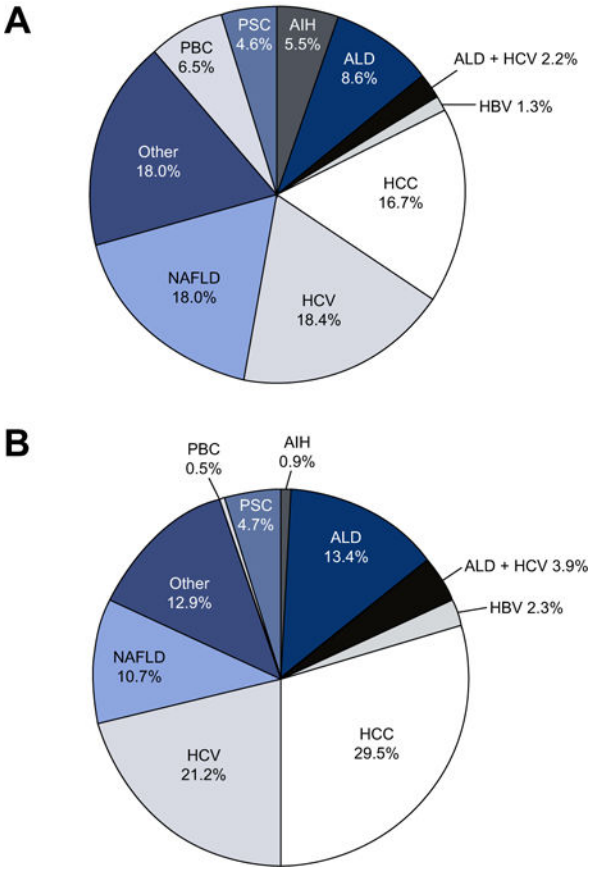
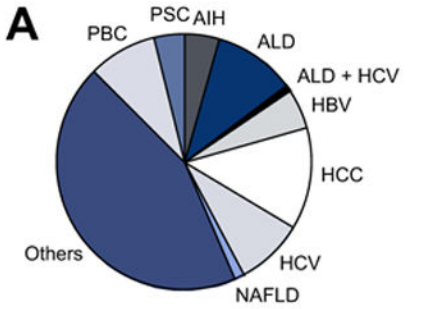
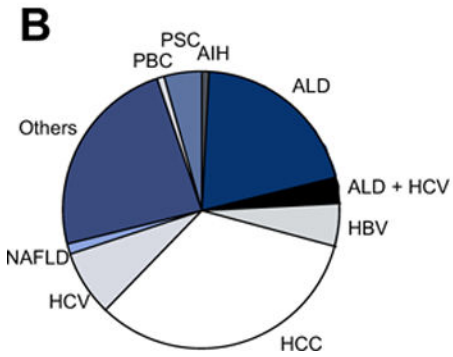


Fig. 3. Indications for liver transplantation in 2013 in the US by sex

(A) Indications for liver transplants in 2013 among U.S. women based on UNOS data. (B) Indications for liver transplants in 2013 among U.S. men based on UNOS data. ALD, alcohol liver disease; PBC, primary biliary cirrhosis; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; HBV, hepatitis B virus; NAFLD, non-alcoholic fatty liver disease.



	Number	Percentage
AIH	77	4.46
ALD	181	10.49
ALD + HCV	12	0.69
HBV	85	4.92
HCC	228	13.21
HCV	148	8.57
NAFLD	22	1.27
Others	761	44.09
PBC	148	8.57
PSC	64	3.71
Total	1726	100



	Number	Percentage
AIH	35	0.98
ALD	724	20.26
ALD + HCV	113	3.16
HBV	176	4.93
HCC	1184	33.14
HCV	275	7.70
NAFLD	39	1.09
Others	842	23.57
PBC	28	0.78
PSC	157	4.39
Total	3573	100

Fig. 4. Indications for liver transplantation in 2012 in Europe by sex

(A) Indications for liver transplants in 2012 among European women based on ELTR data.

(B) Indications for liver transplants in 2012 among European men based on ELTR data (data kindly provided by V. Karam).

Table 1

Key sex differences in waitlist outcomes in the post-MELD era.

Waitlist times and transplant rates	• Women spend longer on waitlist [2-4,7-9] • Transplant rates are higher in men [7-9]
Waitlist mortality	• Many studies note higher mortality [7,12,13] in women, but not all [9]
Size	• Patient height/liver volume contribute to sex disparity in transplant rates and waitlist mortality [6,13]
Renal function	• Waitlisted women have lower creatinine for similar degree of renal failure [8,12,14-16] • Creatinine and MELD scores inadequately reflect renal dysfunction in women
Sarcopenia	• Sarcopenia is strongly associated with waitlist mortality • Women may have lower risk of sarcopenia [35]

Table 2

Sex differences in overall post LT outcomes.

Outcome	Sex difference	Comment
Patient/graft survival	Controversial	German study identified higher 90-day mortality in women [20]. U.S. study did not identify sex difference [21]
Rejection risk	No	No overall sex difference in acute or chronic rejection [29-31] though higher risk of early acute rejection in women with HCV [28]. Women less likely to wean from IMS and develop immune tolerance [25]
Quality of life	Yes	Considerable variability in the definition of specific QOL indicators though differences in sexual function, emotional and physical well-being are apparent
Renal function	Yes	Women at higher risk of CKD post LT [16,32-34]
Post LT recovery and sarcopenia	Yes	In men, but less so women, sarcopenia is associated with worse post LT survival and post operative recovery [36-37]

Table 3

Sex differences in liver transplant by disease.

Liver disease	Epidemiology	Risk of cirrhosis/need for LT	Post-LT outcome
HCV	• Less common in women [67]	• Lower need for LT in women: related to higher spontaneous clearance, lower risk of fibrosis, and less concurrent alcohol use [66-68] • Fibrosis progression may be more rapid in post- than pre-menopausal women [69]	• Women at higher risk of graft loss [72-74] • Possible lower risk of interferon response post LT [75] • No apparent difference in response to new direct acting antivirals • Women at higher risk of early acute rejection [28]
NASH	• NAFLD more common in men • Biopsy proven NASH higher in women [77-79]	• Similar rates of fibrosis in men and pre-menopausal women [81-82]. Fibrosis progression may be more rapid in post-than pre-menopausal women [80] • Similar transplant rates [78]	Similar rates of recurrent disease, patient, and graft survival [83-86]
ALD	• Less common in women [90,92,93]	• Women at higher risk of cirrhosis with lower doses of alcohol exposure [87] • Men account for 75% of transplants for ALD [78]	• Similar patient and graft survival [91-94] • Recidivism controversial: may be higher in women [95-96]
AIH	• More common in women, sex ratio 3.6:1 [97]	• Controversial: male sex predictive of death or need for LT [98-99] • Women with AIH at lower risk for HCC [98]	• Similar post LT survival, recurrent AIH, and risk of rejection [101-103]
PBC	• 90% diagnosed in women [104]	• Women more responsive to ursodiol [108] • Women have less progressive disease [101,106,107] • Women with PBC at lower risk for HCC [109-112]	• Similar risk of recurrent PBC and rejection [101,113] • Limited data on post LT survival differences
PSC	• 60% diagnosed in men [114]	• Controversial: Most studies show no difference in transplant-free survival [115,116] • One study found female sex predictive of death or need for liver transplant [117]	• Similar risk of recurrent PSC [120-122] and rejection [101] • Limited data on post LT survival differences